A 1,5-O→N Carbamoyl Snieckus–Fries-type Rearrangement

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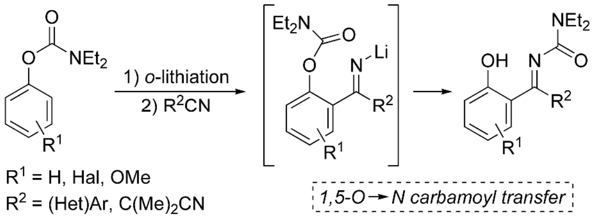
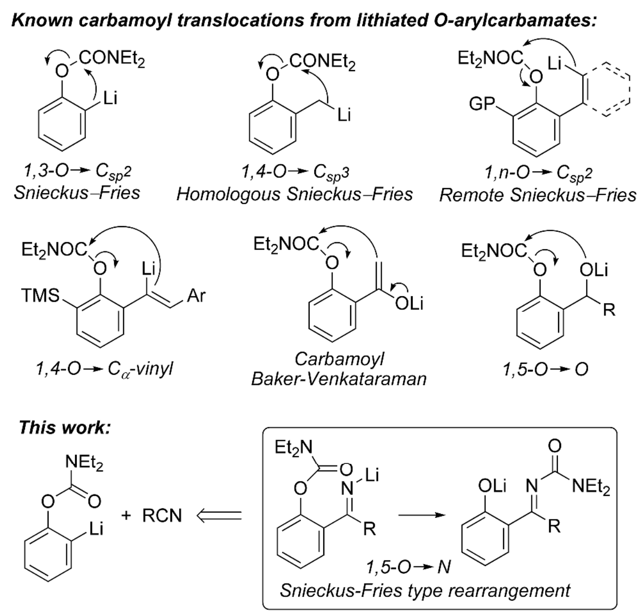
Supporting Information Placeholder



ABSTRACT: The reaction of *o*-lithiated *O*-aryl *N,N*-diethylcarbamates with (hetero)aromatic nitriles gives rise to functionalized salicylidene urea derivatives in high yields through a new 1,5-O-to-N carbamoyl migration. This Snieckus–Fries-type rearrangement nicely complements previously known O-to-C and O-to-O related shifts. In addition, when dimethylmalononitrile is used as the electrophilic partner, the carbamoyl shift is preferred over the expected transnitrilation reaction.

From the pioneering work of Gilman and Wittig, the Directed *ortho* Metalation (D*o*M) reaction has become an essential tool for organic synthesis in the context of accessing regioselectively functionalized aromatic compounds.[1] In this field, *O*-aryl carbamates are one of the most powerful and useful directed metallating groups (DMG), as very low temperatures are needed for their lithiation, and in addition, deprotection to the corresponding phenol derivatives is easily achieved after the corresponding functionalization.[2] The *o*-lithioaryl *N,N*-dialkylcarbamate intermediates are not stable with the increase of the temperature evolving through the anionic version of the Fries rearrangement, also known as the Snieckus–Fries rearrangement.[3] It consists of a O→C 1,3-carbamoyl shift that affords salicylamide derivatives and has led to the development of a variety of synthetic applications.[4] The easiness of this carbamoyl translocation depends on the substituents both on the nitrogen atom and on the aromatic ring, but for the most used *N,N*-diethylcarbamates it typically takes place when raising the temperature from −78 ºC to room temperature following the *o*-lithiation.[5] Along the years, different O→C carbamoyl transfer reactions have been described, mainly by Snieckus and co-workers, including the homologous anionic *ortho*-Fries,[6] the remote anionic Fries,[7] the 1,2-Wittig vs. 1,5-O→C,[8] and the anionic O→$C_{\alpha/\beta}$-vinyl carbamoyl translocations,[9] as well as the carbamoyl version of the Baker–Venkataraman rearrangement.[10] Whereas the anionic *N*-Fries rearrangement involving *N*-carbamoyl N→C translocations are also known,[11] much less developed are the corresponding O→heteroatom carbamoyl transfer processes, and to the best of our knowledge, a few examples of 1,5-O→O rearrangements have been described (Scheme 1).[12]

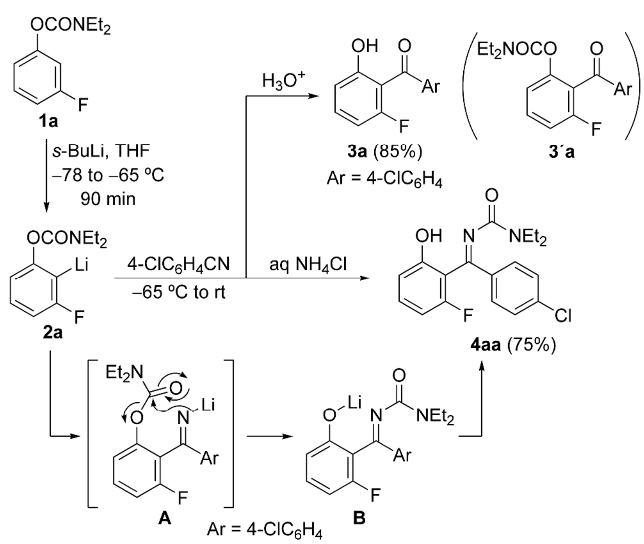
Scheme 1. Rearrangements of Lithiated *O*-Aryl *N,N*-Diethylcarbamates



Following our interest in the development of synthetic methodologies based on the application of D*o*M reactions,[13] herein, we would like to report a new 1,5-O→N carbamoyl migration, a Snieckus–Fries-type rearrangement, that gives access to new and interesting urea derivatives from the reaction of *o*-lithiated carbamates with nitriles.

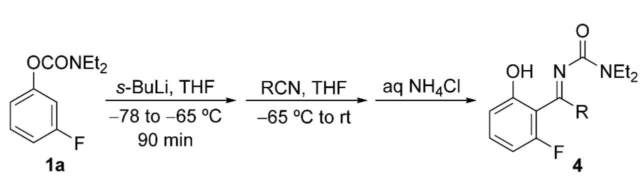
In the past few years, we have been interested in the *o*-lithiation of *O*-3-halo and *O*-3,n-dihalophenyl *N,N*-diethylcarbamates and the study of the reactivity of the corresponding *o*-lithiated species.[14] In this context, and due to the relevance of 2-hydroxybenzophenones as motifs that are present in different biologically active compounds,[15] we were interested in preparing 6-halo-2-hydroxybenzophenone derivatives. To this goal, we tested the reaction of organolithium intermediate **2a**, easily generated from *O*-3-fluorophenyl carbamate **1a**, with 4-chlorobenzonitrile. After acidic hydrolysis, we obtained directly 2-hydroxybenzophenone **3a** in high yield, instead of the expected carbamate **3´a** (Scheme 2). Considering this unexpected result, we carried out the hydrolysis with aqueous NH_4Cl, and surprisingly, the *N,N*-diethyl urea derivative **4a** was selectively obtained in good yield. To account for its formation, we propose that after the initial attack of the *o*-lithiated species **2a** to the cyano group, an intermediate *N*-lithiated imine **A** is generated. This evolves through an intramolecular 1,5-O→N carbamoyl translocation affording phenoxide **B**, which leads to the final urea derivative **4a** upon hydrolysis (Scheme 2).

Scheme 2. Preliminary Results



Choosing carbamate **1a** as a model, we evaluated the scope of this new 1,5-O→N carbamoyl translocation with regard to the nitrile moiety. As shown in Table 1, a variety of (hetero)aromatic nitriles efficiently participate in this process giving rise to benzylidene ureas **4** in good to high yields. Electron-withdrawing groups such as halogens were well tolerated, regardless of their position (entries 1, 2, 6, and 7). In the same way, benzonitriles bearing electron-donating groups can also be used as the electrophilic partners (entries 3 and 4). Heteroaromatic nitriles were also tested, and whereas 4-cyanopyridine efficiently afforded urea **4ah** (entry 8), when 2-furonitrile was employed, a competitive acid-base process likely lowered the yield of **4ai** (entry 9). Finally, aliphatic nitriles, such as cyclopropyl cyanide (entry 10) or allyl cyanide, were investigated leading to the recovery of starting carbamate, probably due to a competitive proton abstraction.

Table 1. Reaction of Carbamate 1a with Nitriles. Synthesis of Urea Derivatives 4

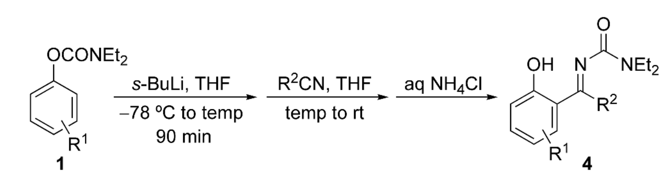


entry	R	product	yield (%)[a]
1	4-ClC_6H_4	**4aa**	75
2	4-FC_6H_4	**4ab**	90
3	4-$MeOC_6H_4$	**4ac**	82
4	4-$MeSC_6H_4$	**4ad**	88
5	Ph	**4ae**	88
6	2-BrC_6H_4	**4af**	77
7	3,5-$Cl_2C_6H_3$	**4ag**	71
8	4-(C_5H_4N)[b]	**4ah**	85
9	2-(C_4H_3O)[c]	**4ai**	42[d]
10	*c*-C_3H_5	–[e]	–

[a] Yield of isolated product referred to starting carbamate **1a**. [b] 4-Cyanopyridine was used. [c] 2-Furonitrile was used. [d] ca. 40% of starting carbamate was recovered. [e] Starting carbamate **1a** was recovered.

Having established the variety of nitriles that can be used for the carbamoyl transfer, we then studied the scope of the reaction with regard to the aryl carbamate moiety. We treated a variety of *o*-lithiated halo- and methoxy-functionalized *O*-aryl *N,N*-diethylcarbamates **1b-j**, with a selection of aromatic nitriles as electrophilic reagents. Gratifyingly, we found that both types of substituents on the aryl moiety of the starting carbamate are compatible with the rearrangement, as the expected benzylidine urea derivatives **4** were obtained in all cases with high yields (Table 2). Interestingly, we found that with all the carbamates **1** we could use *s*-BuLi as metallating reagent, except for 3-bromophenyl carbamate **1d** in which LDA was employed, without any other additive by careful control and adjustment of the reaction temperature. In this way, highly interesting benzylidene ureas **4** bearing halogen and alkoxy substituents, apart from the free hydroxyl group, have been easily and efficiently accessed from simple *O*-aryl *N,N*-diethylcarbamates **1**.[16]

Table 2. Reactions of *O*-Aryl *N,N*-Diethylcarbamates 1 with Selected Nitriles



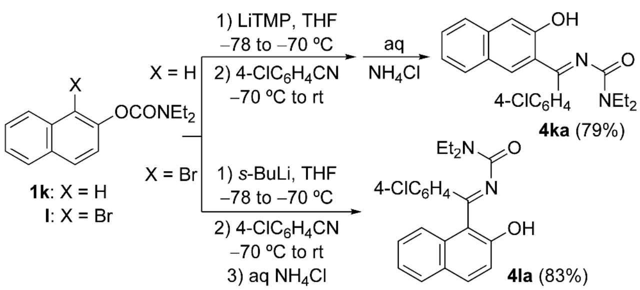
entry	1	R^1	temp (ºC)	R^2	product	yield (%)[a]
1	**1b**	H	–78	4-ClC_6H_4	**4ba**	72
2	**1b**	H	–78	4-$EtOC_6H_4$	**4bj**	71
3	**1c**	3-Cl	–65	4-ClC_6H_4	**4ca**	79
4[b]	**1d**	3-Br	–78	4-ClC_6H_4	**4da**	75
5[b]	**1d**	3-Br	–78	4-$MeOC_6H_4$	**4dc**	80
6	**1e**	4-Cl	–70	4-ClC_6H_4	**4ea**	82
7	**1e**	4-Cl	–70	2-FC_6H_4	**4ek**	86
8	**1f**	4-F	–65	4-ClC_6H_4	**4fa**	81
9	**1g**	2-Cl	–70	4-ClC_6H_4	**4ga**	87

10	**1h**	4-MeO	–70	4-ClC_6H_4	**4ha**	83
11	**1h**	4-MeO	–70	2-FC_6H_4	**4hk**	85
12	**1i**	2-MeO	–70	4-ClC_6H_4	**4ia**	83
13	**1i**	2-MeO	–70	4-$EtOC_6H_4$	**4ij**	74
14	**1j**	3,4-Cl_2	–65	4-ClC_6H_4	**4ja**	79

[a] Yield of isolated product referred to starting carbamate **1**. [b] LDA was used instead of *s*-BuLi.

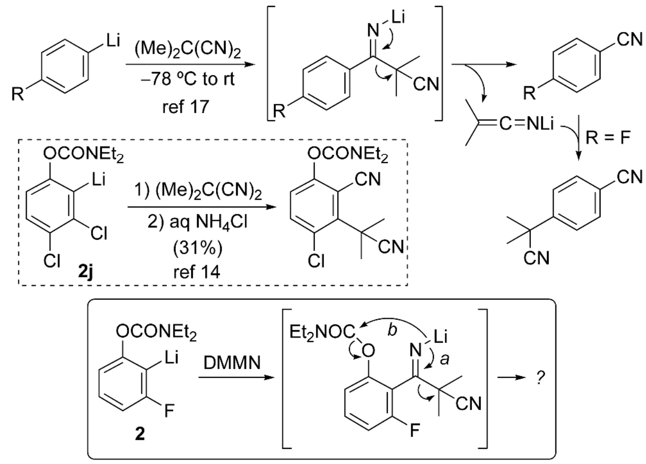
O-Naphth-2-yl carbamates **1k,l** also provide facile entry to diarylmethylene urea derivatives **4ka** and **4la** (Scheme 3). However, in order to achieve regioselective lithiations two independent routes were followed. The *O*-naphth-2-yl carbamate **1k** could be regioselectively lithiated at C-3 with LiTMP,[17] as described by Snieckus and co-workers. On the other hand, for reaching C-1 selective lithiation, *O*-(1-bromo-2-naphth-2-yl) carbamate **1l** was used. In both cases, the desired 1,5-O→N carbamoyl migration efficiently took place leading to the corresponding (hydroxynaphthalenyl)methylene urea **4ka** and **4la** in high yields (Scheme 3).

Scheme 3. Selective Synthesis of Ureas 4ka and 4la from *O*-Naphth-2-yl *N*,*N*-Diethylcarbamates 1k and 1l



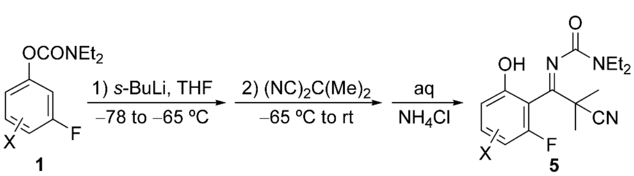
On the other hand, Reeves and co-workers had reported the electrophilic cyanation of aryl Grignard or lithium reagents by transnitrilation with dimethylmalononitrile (DMMN).[18] More recently, they have also developed the 1,4-difunctionalization of the corresponding 4-fluoro-magnesium or lithium reagents via a subsequent S_NAr reaction with the isobutyronitrile anion expelled from the initial transnitrilation (Scheme 4).[18b] In our previous report,[14] we had described a few examples of the 2,3-difunctionalization of *O*-(3-chlorophenyl) carbamates, such as **1j**, which led to dicyano-functionalized *O*-arylcarbamates derived from a transnitrilation–S_NAr reaction, although in low to moderate yields. At this point, we decided to react a variety of *O*-(3-fluorophenyl) carbamates **1a,m-p** with DMMN with the aim of studying which of the two competitive processes, sequential transnitrilation–S_NAr reaction (via *a*) vs. the 1,5-O→N carbamoyl rearrangement (via *b*), would be favoured (Scheme 4).

Scheme 4. Reaction of Aryllithiums with DMMN,[17] and Proposal for *o*-Lithiated *O*-Arylcarbamates 2



With all the assayed *O*-3-fluorophenyl *N*,*N*-diethylcarbamates **1a,m-p**, bearing one or two fluorine atoms or one fluorine and one chlorine atoms (Table 3), we isolated cyano-functionalized urea derivatives **5** in high yields, which keep the original halide substituents in their structures. Interestingly, the obtained results indicate that the carbamoyl migration (via *b* in Scheme 4) is faster than the competitive retro-Thorpe-type reaction (via *a*). It is interesting to note that compounds **5** are highly functionalized substrates bearing one or two halogen atoms, a tertiary cyano group, and a free hydroxyl group on the salicylidene urea moiety.

Table 3. Reaction of Carbamates 1 with DMMN. Synthesis of Cyano-functionalized Urea Derivatives 5

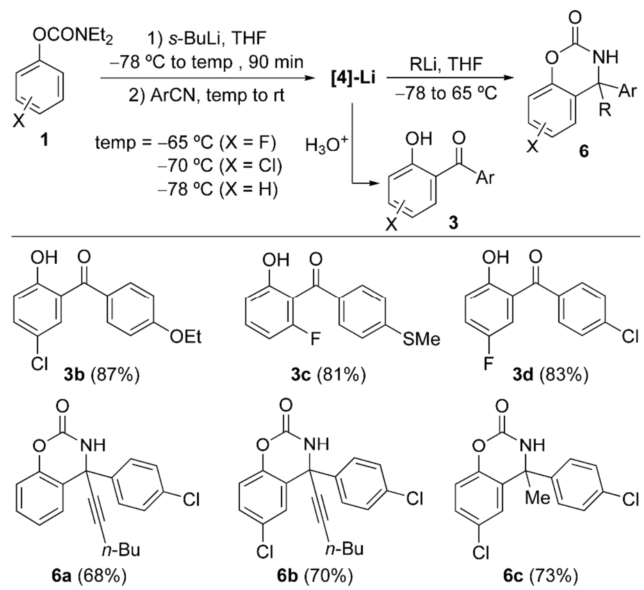


entry	carbamate	X	product	yield (%)[a]
1	**1a**	H	**5a**	84
2	**1m**	4-F	**5b**	74
3	**1n**	2-F	**5c**	75
4	**1o**	4-Cl	**5d**	78
5	**1p**	3-Cl	**5e**	71

[a] Yield of isolated product referred to starting carbamate **1**.

To further show the potential usefulness of the benzylidene urea derivatives **4**, we carried out different transformations, some of them in situ. As initially established in Scheme 2, acidic hydrolysis of the reaction of *o*-lithiated carbamates **2** with selected nitriles afforded *o*-hydroxybenzophenones **3** in high yields (Scheme 5). Interestingly, if prior to the hydrolysis the crude lithium phenoxide intermediate is treated with an excess of organolithium reagents, such as hex-1-ynyllithium or methyllithium, the new benzo[1,3]oxazin-2-ones **6** are obtained, bearing a quaternary center at C-4. Their formation could be understood by a tandem nucleophilic addition of the organolithium to the C=N bond of the benzylidene urea, followed by the attack of the lithium phenoxide to the carbonyl group of the urea (Scheme 5).[19]

Scheme 5. Further Transformations of Ureas 4



In summary, we have reported a new O-to-N carbamoyl rearrangement that takes place in the reaction of *o*-lithiated carbamates with nitriles. It provides a general regioselective entry into sterically encumbered and highly functionalized salicylidene urea derivatives. In addition to aromatic nitriles, dimethyl malononitrile is also able to participate in this carbamoyl transfer, avoiding the previously reported retro-Thorpe-type reaction in the intermediate imine, which otherwise leads to cyanation of the organolithium. In addition, regioselectively functionalized *o*-hydroxybenzophenones and benzoxazinones, have also been synthesized in one-pot processes, taking advantage of the intermediate salicylidene ureas.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and copies of NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing interest.

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(19) It is interesting to note that the cyclization of the phenoxide onto the urea happens only after nucleophilic attack on the C=N bond and not before, likely due to an (*E*)-configuration of the C=N bond in benzylidene ureas **4**.